Pediatric Cardiology and Cardiovascular Surgery: 1950–2000

Robert M. Freedom, MD, FRCPC; James Lock, MD; J. Timothy Bricker, MD

For those caring for the patient with congenital heart disease, the last 50 years of the 20th century was witness to staggering advances in virtually all aspects of pediatric cardiovascular medicine and surgery. The first half of the 20th century was not dormant in this regard. Dr Maude Abbott of Montreal had published her wonderful atlas in 1936 under the auspices of the American Heart Association, a unique compilation of 1000 cases of congenital heart disease.1 Dr Helen Taussig of Baltimore had founded her cardiac clinic at Johns Hopkins and had begun in the 1930s to characterize the clinical and fluoroscopic findings of a wide variety of congenital heart malformations; this material matured into her 2-volume compendium on congenital heart disease published in 1960.2 Dr Robert E. Gross of the Children’s Hospital in Boston successfully ligated the patent arterial duct in 1938, and that signal accomplishment ushered in the era of surgery for congenital heart disease.3 On the basis of her clinical observations that some children with cyanotic congenital heart disease became progressively more cyanotic coincidently with closure of the arterial duct and cognizant of Gross’s benchmark contribution, Dr Taussig traveled to Boston to attempt to persuade him to construct an arterial duct. When he refused, she broached the subject to Dr Blalock at Johns Hopkins. Some years earlier, when in Vanderbilt and with the technical assistance of Vivien Thomas, in an attempt to produce pulmonary hypertension and using the dog as the experimental animal, Dr Blalock constructed an end-to-end surgical anastomosis between the subclavian artery and the pulmonary artery. With Dr Alfred Blalock as the surgeon and the wisdom of his assistant Vivien Thomas, Taussig and Blalock revolutionized the care of the cyanotic child with the construction of the subclavian artery–to-pulmonary artery end-to-side anastomosis, thus augmenting pulmonary blood flow, and published their early experience in 1945.4 Coarctation of the aorta was successfully repaired in 1945 by Crafoord and Nylin of Stockholm5; Brock, using a “closed” technique, performed a pulmonary valvotomy6; and in 1950, Blalock and Hanlon performed an atrial septectomy using the surgical clamp designed by Vivien Thomas.7 And then came the last half of the 20th century.

Perinatal Cardiac Physiology

An understanding of the physiology of the unique aspects of the circulation of the fetus and neonate, as well as the concept of the transitional circulation, had a profound impact on the development of treatment modalities in pediatric cardiology.8–10 Basic understanding of developmental cardiovascular physiology allowed a number of medical and surgical advances in the care of infants with heart disease. Research regarding the distribution of blood flow in the fetus and the changes in flow and in vascular channels at the time of birth led to the concept of the persistent fetal circulation (or persistent transitional circulation). These babies were often mistaken for babies with significant structural cardiac malformations, and attempts at definitive diagnosis or intervention could be disastrous. The relative contribution of changes in stroke volume and heart rate in the potential for providing cardiac output reserve of the neonate compared with the adult led to insights of profound importance in neonatal cardiac care. Research that led to an understanding of myocardial perfusion in the developing heart and the unique metabolic aspects of the neonatal heart opened the way for efficient cardioplegia and myocardial protection, pharmacological circulatory support, and neonatal cardiac resuscitation.

Rudolph and his colleagues, among many others, have fully characterized the fetal circulation, demonstrating flow patterns of the great veins; the fetal channels, including the ductus venosus and the arterial duct; and the obligatory right-to-left shunting at the level of the foramen ovale occurring in the fetus.8–10 The nature of the combined ventricular output in the fetal lamb has been determined, and the relative distributions of flow to the collapsed and unaerated lungs, as well as to the various components of the aortic arch, the transverse aortic arch, and the isthmus. Those complex overlapping changes responsible for the normal functional and anatomic closure of the arterial duct have also been elucidated. In part, the understanding of the pharmacological and physiological manipulation of the arterial duct led to the development of prostanoid therapy and to biological manipulation of the arterial duct. Many have shown that the contractility or force generated by fetal myocardium is less than that generated by adult myocardium. There is evidence

From the Division of Cardiology, Department of Pediatrics, the Hospital for Sick Children and University of Toronto Faculty of Medicine (R.M.F.); the Department of Cardiology, the Children’s Hospital and Harvard Medical School, Boston (J.L.); and the Lillie Frank Abercrombie Section of Cardiology, Department of Pediatrics, Baylor College of Medicine and Texas Children’s Hospital, Houston, Tex (J.T.B.).

Correspondence to Robert M. Freedom, MD, The Hospital for Sick Children, 555 University Ave, Room 1503, Toronto, Ontario, Canada M5G 1X8.
E-mail rfreedom@sickkids.on.ca

(Circulation. 2000;102:IV-58–IV-68.)
© 2000 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

IV-58
that many of the subcellular elements of the contractile response in the fetus are relatively immature and that a substantial increase in β-adrenergic receptor concentration takes place after birth. The factors responsible for the increase in β-adrenergic receptor concentration are not completely understood, but certainly thyroid hormone has a substantial role. The role of afterload in the fetal heart and the response of global ventricular function to a changing heart rate have also been studied in detail. Many have been interested in these perinatal changes, especially as they manifest themselves in so-called disturbances of the transitional circulation, including persistent fetal circulation or transitional myocardial ischemia of the newborn, the latter a phenomenon fully characterized by the late Richard Rowe. The central fetal circulation changes dramatically at birth. The inefficient separation of the oxygen uptake and delivery circulations of the fetus is replaced by 2 distinct circulations in series after birth. This parallel circulation is achieved by closure of the arterial duct and the ductus venosus, the separation of and from the umbilical circulation, and the cessation of the right-to-left flow or shunting through the foramen ovale. Coincident with these changes is a substantial increase in pulmonary blood flow and an increase in output from each ventricle. Clearly, ventilation, oxygenation, and umbilical cord occlusion are the gross events responsible for the transition from the fetal circulatory pattern to the circulatory pattern of the newborn. These phenomena are mediated by a complex tapestry of neurohumoral, mechanical, and environmental factors. The structure and function of the arterial duct and its physiological and pharmacological manipulation led both to the development of indomethacin therapy to promote functional and anatomic closure and to prostanooid therapy to maintain ductal patency. The biological mechanisms responsible for duct closure have led to its novel biological manipulation (see below).

Cardiac Anatomy and the Nosology of Congenital Heart Disease

The contributions of Drs Maurice Lev of the Hektoen Institute; Jesse Edwards of the Mayo Clinic and the Charles T. Miller Hospital; Richard Van Praagh of Toronto, Chicago, and then Boston; Robert H. Anderson of London; and Anton Becker of Amsterdam, among others, must be singled out as critically important to the foundation of congenital heart disease: the study of congenitally malformed hearts.11–28 With their clinical colleagues, they compiled clinicopathological correlations and published extensively on specimens that constituted their cardiac registries. Collectively, they described and characterized the entire spectrum of congenitally malformed hearts and produced a number of classifications of various cardiac anomalies, including tricuspid atresia, interruption of the aortic arch, truncus arteriosus, ventricular septal defect, double-inlet ventricle, and double-outlet right ventricle.

Although all of the cardiac morphologists mentioned above and their respective colleagues concentrated on descriptive anatomy and definition of unifying morphological features, Lev, Anderson, and Becker also provided detailed information about the specialized conduction tissue in the normal and malformed heart, with special emphasis on the conduction system of hearts with congenitally corrected transposition of the great arteries and “single”-ventricle malformations.

One of the many conundrums facing those caring for patients with congenital heart disease was the issue of classification and thus communication. In an attempt to wrest clarity from chaos, Richard Van Praagh and his colleagues, in a series of important articles beginning in the early 1960s from Toronto and then from Boston, provided the framework for the segmental analysis of congenital heart disease.11–17 Three segments were identified: the atria, the ventricular loop (d or l), and the great arteries. By use of deductive morphology, the various segments could be connected. Van Praagh and his colleagues emphasized in their many publications the conal or infundibular anatomy of the hearts under discussion, fully characterizing the conal anatomy of normal hearts, hearts with tetralogy of Fallot, truncus arteriosus, complete and corrected transposition of the great arteries, isolated ventricular inversion, anatomically corrected malposition of the great arteries, etc. Eschewing a “deductive” approach to segmental analysis, Dr Robert Anderson and his colleagues from the United Kingdom, using a segmental approach, advocated a sequential “connections” approach.22–24 This approach did not focus on infundibular anatomy, and their initial approach did not use the concept of ventricular loops, nor did their approach incorporate the bracketed shortcut alphabet nomenclature. These 2 schools of cardiac nomenclature were initially quite polarized, and although they share many similarities, their differences have not been completely resolved. Thus, these 2 schools of cardiac nomenclature are now widely used by the loyal disciples of each. As yet, the “Esperanto” of congenital heart disease has not been fully realized, although many use an amalgam of the 2 schools.27

Cardiac Catheterization and the Calculation of Pulmonary Vascular Resistance

Right heart catheterization, first performed in the late 1940s, matured in the 1950s to left heart catheter investigations, with the left heart entered through preexisting defects in the atrial or ventricular septum or from the retrograde arterial approach.29–32 The determination or measurement of oxygen saturation in the various heart chambers allowed for calculation of left-to-right shunt, right-to-left shunt, and effective pulmonary blood flow. The application of the Fick principle permitted calculation of the pulmonary vascular resistance. The calculated pulmonary vascular resistance could be correlated with clinical features and outcome of surgery or no surgical intervention. The correlation of calculated pulmonary vascular resistance with the histological determination of pulmonary vascular disease also provided important information.

An understanding that pulmonary vascular resistance helps determine pulmonary blood flow in patients with congenital cardiac malformations.33–36 In 1950, it was not understood which patients with large ventricular septal defects would survive surgery and when the elevated pulmonary artery pressure would come down after ventricular septal defect closure. The concept of high pulmonary pressure from high flow in some patients and high resistance was hardly intui-
tive. Calculation of pulmonary vascular resistance led to an understanding of pulmonary vascular obstructive disease, to better patient selection for heart surgery, and to optimal timing of operative intervention. Ultimately, this also led to pharmacological interventions for elevated pulmonary vascular resistance.

**Diagnosis of Congenital Heart Disease**

Cardiac catheterization became a reality in the 1940s, and right heart and then left heart cardiac catheterization became a reality for infants and children in the 1940s and 1950s.\(^{36-48}\) Single fixed-plane angiographic equipment evolved to bi-plane equipment, and by the 1970s, at least one plane was movable.\(^{32,37,45,48}\) Cut-film technique evolved to cineangiograms, from 16 mm to 35 mm. Bargeron and his colleagues, and others, beginning in the mid 1970s, introduced axial angiography, and these angled views were rapidly assimilated.\(^{39-45}\) Wonderful images were achieved with large-bore catheters and “adequate” amounts of contrast delivered rapidly by pressure injectors. From cine technique, now studies are archived on CDs, and many facilities store and archive in a “cineless” environment. M-mode echocardiography of the 1970s gave way to cross-sectional imaging in the early 1980s. Sahn, Silverman, Williams, Huhta, Smallhorn, and others catalogued the diagnostic features of the entire spectrum of congenital heart malformations.\(^{49-53}\) Color Doppler technology added yet another dimension to this noninvasive imaging modality. In many centers, cross-sectional echocardiography replaced cardiac catheterization and angiography as the primary diagnostic tool, and cardiac operations were planned and executed on the basis of echocardiography. Thus, imaging algorithms for the patient with congenital heart disease, as in the patient with acquired heart diseases, continue to evolve, with more and more information gleaned noninvasively. The transesophageal approach to cross-sectional echocardiography has now been extended to very small infants, with some probes used in infants of 2 to 3 kg, and this intraoperative approach has dramatically reduced the need for immediate postoperative reoperation. Contrast echocardiography, cardiac CT, MRI, single photon emission CT perfusion imaging, stress echocardiography, tissue Doppler characterization, 3D echocardiography, PET, and intravascular ultrasound are but some of the newer imaging tools.\(^{54}\) With these modalities, used in isolation or in combination, considerable information about cardiac structure, function, myocardial perfusion, and tissue characterization can be obtained. Fetal echocardiography has provided a new frontier for diagnosis, counseling, and treatment. Certainly the last 15 years of the 20th century can be seen as the apogee of cross-sectional echocardiographic imaging. From the 1950s onward, large textbooks devoted to the practice of pediatric cardiology and its subspecialty areas were published.

**The Prostaglandin Story**

Clinical trials to manipulate the patency of the ductus arteriosus with pharmacological agents arose directly from the basic research in cardiovascular development.\(^{55-65}\) Maintaining patency of the ductus arteriosus with prostaglandin E\(_1\) has profoundly changed the potential for intervention for babies with many serious structural heart malformations. This treatment option potentially impacts the care of neonates with critical left-sided obstructive lesions and with transposition physiology as well as that of cyanotic newborns whose only source of pulmonary blood is the ductus arteriosus. The impact has been to lower mortality and allow planned operations to replace desperate and frantic attempts at emergency palliations. Preoperative evaluation has become more thorough and safer because of this treatment. Pharmacological ductal closure in the premature with indomethacin provided an option to avoid high-risk cardiovascular operations in this group of babies.

The “bench-to-bedside” paradigm of prostanoid therapy is a wonderful story that is founded in the physiology of the arterial duct. The role of the arterial duct in the “normal” circulation of the fetus and in the transitional circulation was unraveled by Abraham Rudolph and his colleagues and many others.\(^{62}\) They clearly defined those physiological parameters to which the arterial duct responded and helped to clarify pharmacological manipulations that could lead to ductal constriction and closure or to persistent patency. Coceani and Olley, among others, demonstrated in the lamb model that patency of the arterial duct could be maintained through administration of an E-type prostaglandin.\(^{55-57}\) From the laboratory animal, an E-type prostaglandin was initially used in the patient with duct-dependent pulmonary blood flow, and then the indications were rapidly extended to the patient with duct-dependent systemic blood flow, including neonates with hypoplastic left heart syndrome, coarctation of the aorta, interruption of the aortic arch, and neonatal critical aortic stenosis. It was clinically evident that ductal patency in the neonate with complete transposition of the great arteries was an advantage, and thus prostanoid therapy was offered to this group of patients as well. By the mid to late 1970s, prostaglandin therapy was firmly entrenched in the therapeutic algorithm of a wide range of patients. Not unexpectedly, a host of potential complications associated with prolonged administration of prostaglandin therapy emerged as well.\(^{58,66-73}\) The functional and physiological manipulation of the arterial duct of the last quarter of the 20th century will soon be history. Functional and anatomic closure of the arterial duct requires prenatal formation of intimal cushions. Their formation requires fibronectin-dependent smooth muscle migration. Mason and her colleagues from the laboratory of Dr Marlene Rabinovitch in Toronto have shown that in the fetal lamb, if the fibronectin mRNA binding protein was sequestered, fibronectin translation was inhibited and intimal cushion formation prevented, thus promoting persistent patency of the arterial duct.\(^{74}\) Thus, in slightly more than 60 years, we have witnessed the following accomplishments: surgical closure of the arterial duct, construction of an arterial duct (the Blalock-Taussig shunt), unraveling the physiology of the arterial duct and its pharmacological manipulation, the prostaglandin story, catheter closure of the arterial duct, and biological manipulation of the arterial duct.
Catheter-Based Therapy in Congenital Heart Disease

Rubio-Alvarez et al, in 1953, described the technique by which pulmonic stenosis could be relieved by a catheter technique. A quarter of a century later, Semb et al, using an inflated balloon-tipped angiographic catheter, ruptured the valve when the catheter was withdrawn from the main pulmonary artery to the right ventricle, reducing the outflow gradient. However, it was the introduction of static balloon dilation by Kan and her colleagues that fostered the application of this therapeutic modality to a greater audience. Over the past 2 decades, the technique has become the "treatment of choice" for pulmonary valve stenosis at any age and with any valve morphology. The safety and efficacy of the technique in infants, children, and adolescents has been confirmed by numerous studies summarized by McCrindle and Kan. But catheter-based therapy for congenital heart disease was clearly focused by the then novel approach of Rashkind and Miller, who in 1966 demonstrated the role of balloon atrial septostomy as a maneuver to promote mixing at the atrial level in the patient with complete transposition of the great arteries. The application of this technique forever changed the outcome for patients with transposition of the great arteries and was immediately assimilated into the therapy of the neonate with transposition and inadequate mixing. Soon, the approach was extended to patients with obligatory right-to-left shunting at the atrial level and to those with obligatory left-to-right shunting at the atrial level, where atrial restriction was clinically important. Porstmann et al first advocated a percutaneous technique for permanent closure of the arterial duct, which could be achieved via the femoral artery, in the late 1960s, but this technique was not widely used. Closure was accomplished with an Ivalon (polyvinyl alcohol) plug introduced by catheterization from the femoral artery. The 1980s were witness to a virtual explosion of catheter-based therapy. Balloon dilatation was offered to patients with aortic stenosis, valvar and subvalvar; native and recoarctation of the aorta; pulmonary arterial stenosis, acquired and congenital; and to a wide range of acquired obstructions (Mustard or Senning baffles, etc.). Catheter closure of the arterial duct with any of a variety of catheter-delivered devices or coils became standard practice, as did closure of the atrial septal defect or foramen ovale. In the late 1980s and throughout the 1990s, there was increasing experience with catheter closure of the muscular ventricular septal defect. Lock in Boston, Mullins in Texas, Tynan and Quereshi in London, Benson in Toronto, and their respective colleagues pioneered many of these applications, but certainly the Boston and Houston groups paved "the yellow brick road." Today, fistulae in the coronary, systemic, and pulmonary circulations are often addressed primarily with catheter-based therapy. Other applications of these techniques include dilatation of the pulmonary outflow tract in tetralogy of Fallot and wire or radiofrequency perforation of the pulmonary valve in pulmonary atresia and intact ventricular septum or in the patient with membranous pulmonary atresia and ventricular septal defect. It was soon appreciated that static balloon dilatation of acquired pulmonary arterial stenosis all too frequently did not produce sustained improvement.

The introduction of endovascular stents into the stenotic and hypoplastic pulmonary artery afforded considerable improvement for many patients, and stents have now been implanted in stenotic conduits as a maneuver to delay conduit replacement. Such endovascular stents have now been applied to some patients with native and acquired recoarctation of the aorta, and patients with diffuse aortitis from Takayasu's arteritis have benefited from this therapy. Endovascular stents have been used in some patients with focal hypoplasia of the transverse aortic arch, thus obviating the need for surgery. Stents have been used in the arterial duct, the atrial septum, and pulmonary veins with variable success. Today, there are relatively few areas of the cardiovascular system that have not been explored by the interventional pediatric cardiologist. Stents can be used to rehabilitate obstructed femoral and iliac veins and acquired inferior caval obstruction. One can use stents to widen narrowed baffle channels after Mustard's or Senning's procedures and to improve constricted circuits within a lateral tunnel or extracardiac Fontan. Devices can be used to occlude acquired systemic venous–to–pulmonary venous channels after the Fontan or bidirectional cavo pulmonary shunt or to occlude systemic venous–to–systemic venous connections after a bidirectional cavo pulmonary shunt, such channels reducing the effective pulmonary blood flow. Devices can be used to occlude important aortopulmonary collaterals before any form of intraoperative repair, but especially before Fontan-type surgery. Endovascular stents can be used to widen stenotic aortopulmonary collaterals to palliate some patients with complex pulmonary atresia. The applications and literature have been amply reviewed in books published by Lock et al in 1987 and Rao in 1993. The treatment of a wide variety of tachyarrhythmias has evolved from primarily pharmacological to catheter-based mapping and ablation therapy. How has catheter-based therapy changed the practice of pediatric cardiovascular medicine? At the Toronto Hospital for Sick Children, 903 catheter studies were performed in 1973, and >98% were diagnostic investigations, with the remainder being balloon atrial septostomies and needle aspiration of pericardial fluid. During the same year, 404 cardiac operations were performed, open and closed. In 1985, only 505 catheter procedures were performed in our institution, while nearly 900 operations were carried out. Noninvasive imaging with cross-sectional echocardiography permitted cardiac surgery without angiography in many of these patients. At the conclusion of the 20th century, ~900 operations were performed in our institution, but the catheter numbers had dramatically increased to ~925, with the majority of these procedures now having an interventional or therapeutic role.

Open-Heart Surgery

By 1950, some forms of surgical palliation for congenital heart disease were firmly entrenched. Pulmonary artery banding had been introduced in 1952 as a novel way to control or moderate excessive pulmonary blood flow and pulmonary artery hypertension. The introduction of cardiopulmonary bypass in the mid 1950s and deep hypothermia with circulatory arrest in the early 1970s provided the platform for intracardiac repair of most congenital cardiac
conditions amenable to repair. In the early days of open-heart surgery, the older child underwent primary repair. The young infant was usually palliated with pulmonary artery banding to control excessive pulmonary blood flow and pulmonary artery hypertension, or with some form of systemic-to-pulmonary artery anastomosis to augment pulmonary blood flow. The introduction of deep hypothermia with circulatory arrest in the early 1970s provided the ability to perform primary repair of some defects even in the young infant. It was Castaneda and his colleagues at the Children’s Hospital in Boston who advocated primary repair of most conditions, including ventricular septal defect, tetralogy of Fallot, and interruption of the aortic arch with ventricular septal defect. Patients with common arterial trunk, once palliated with pulmonary artery banding, underwent primary repair in the early 1970s, with a conduit connecting the right ventricle to the pulmonary arteries.

The transition and changing outcome from palliation to repair can be gleaned from experience with babies with complete transposition of the great arteries. From 1950 to 1959, babies with complete transposition of the great arteries were palliated with either a Blalock-Hanlon atrial septectomy or one of the partial venous switch operations pioneered by Baffes, Albert, and others. Mortality for any of these procedures was substantial. Mustard attempted an arterial switch operation with relocation of one coronary artery in the mid 1950s, realizing the advantage of an anatomic repair, but none of his patients survived. The contribution by Senning in 1959 of a complete venous switch is one of the partial venous switch operations was a renaissance of the Senning operation, which was performed in young babies, avoiding any palliation in many. In the next 10 to 15 years after the successful introduction of the Mustard or Senning procedure, a “Pandora’s box” of complications were catalogued, including mechanical complications related to the intra-atrial baffle; sick sinus syndrome and atrial tachycardia and flutter, reflecting damage to the sinus node and its artery; sudden death; and systemic right ventricular dysfunction. In Toronto, % of babies referred to our institution with complete transposition died before Mustard’s operation could be employed. Because of death before Mustard’s operation and ongoing early and late complications, especially in the group of patients with transposition with large ventricular septal defect, there was of course interest in achieving an anatomic repair with coronary artery relocation. Almost 2 decades after the failed attempts of Mustard to perform an anatomic repair, this was finally accomplished in São Paulo, Brazil, by Dr Adib Jatene. By the late 1970s, an arterial switch operation had become the procedure of choice for most patients with transposition of the great arteries with ventricular septal defect. Maneuvers were introduced to prepare the left ventricle of the patient with transposition and intact ventricular septum for the arterial switch when the babies presented after the first month of life. Castaneda and his colleagues in the early 1980s introduced the concept of the neonatal arterial switch, and this soon became the procedure of choice. Thus, the last half of the 20th century was witness to a remarkable change in outcomes for the baby with transposition. With the introduction of the arterial switch operation in Toronto, only % of babies now die before the arterial switch procedure, and for simple transposition the surgical mortality is <2%. What a profound change from the observations of Liebman, Cullum, and Belloc, who addressed the “natural” history of patients with transposition of the great arteries in the era before balloon atrial septostomy and Mustard repair. This is but one of the remarkable sagas in congenital heart disease. Similar drama can be found in the surgical history of tetralogy of Fallot, complex pulmonary atresia with ventricular septal defect, interruption of the aortic arch with ventricular septal defect, the hypoplastic left heart syndrome, and other complex anomalies amenable only to “single” ventricle palliation, among others.

Finally, in the consideration of surgical alternatives, the experience of “Baby Fae” in Loma Linda, Calif, opened the door to cardiac replacement therapy for the hypoplastic left heart syndrome and a wide variety of other congenital and acquired cardiac conditions in the neonate, infant, and older child. Today, in many centers cardiac replacement is a routinely considered form of therapy.

Right Heart Bypass and the Fontan Experience
Glenn, Robiscek, Trusler, and Castaneda, among others, have fully documented the history of those contributions, beginning in the early 1950s with those of Carlon, Mondini, and de Marchi, which led to the successful partial right heart bypass, culminating in the successful application of the classic right-sided cavopulmonary shunt, now known around the world as the Glenn shunt. This experience firmly established the reality that under certain circumstances, a component of the systemic venous return could be conveyed directly into a lung without the interposition of a ventricular pumping chamber. That the classic Glenn shunt provided excellent palliation for many patients is abundantly clear from the literature, although this procedure was not without its early and late complications. Late deterioration could be explained by the development of systemic venous-to-systemic venous collaterals, which reduce effective pulmonary...
blood flow; systemic venous–to–pulmonary venous collaterals, a disadvantageous upper body–to–lower body ratio; or the development of pulmonary arteriovenous malformations. The complication of pulmonary arteriovenous malformations after a classic Glenn anastomosis is well described and was initially attributed to lack of pulsatile blood flow, especially to the dependent portion of the right lung. Experience with the Kawashima operation has now provided another intriguing explanation, namely, exclusion of hepatic venous flow from the pulmonary circulation. But it was the total right heart bypass as conceived and effectively carried out by Fontan and Baudet for 3 patients with tricuspid atresia that provided long-term palliation for patients with heart malformations not amenable to biventricular repair. The criteria for a successful Fontan operation and anatomic indications for this procedure continue to evolve, as have the surgical techniques for a total right heart bypass. From the original atriopulmonary connection with caval valves as used by Fontan, a number of surgical modifications introduced by De Leval in London were used to make the Fontan circulation more energy-efficient. Thus, in many centers, a total cavopulmonary connection, lateral tunnel, or extracardiac Fontan are now routinely used. A number of maneuvers have also been introduced to reduce Fontan mortality, including staging with a bidirectional cavopulmonary shunt with or without atrial fenestration at the time of the Fontan.

A substantial number of complications have been attributed to a Fontan circulation. Some of these certainly challenge the bed-to-bench paradigm, among them, pulmonary arteriovenous malformations, protein-losing enteropathy, and plastic or mucinous bronchitis. This is not the forum to explore all these issues, but a few words about pulmonary arteriovenous malformations are germane. The etiology of pulmonary arteriovenous malformations seems to be greatly increased numbers of thin-walled vessels, but application of immunohistochemical techniques suggests that the rate of cellular proliferation is not increased. It is unclear whether the histological and immunohistochemical markers of the pulmonary arteriovenous malformations in these patients with cyanotic congenital heart disease are the same as in patients with the Weber-Osler-Rendu condition. The incidence of the development of pulmonary arteriovenous malformations in patients with cyanotic congenital heart disease is uncertain, and their ascertainment is in large part methodology-dependent, as shown by Chang and colleagues.

Although the Fontan operation can be carried out in many centers with an operative mortality of <5%, these figures apply only to those undergoing the Fontan, not to the entire cohort. Surgical mortality thus addresses the “tip of the iceberg.” Finally, the names of some inventive surgeons have become firmly entrenched in the pediatric cardiology lexicon: the Glenn shunt; the Fontan operation; the Norwood procedure; the Damus-Kaye-Stansel procedure.

Outcome Analysis in Congenital Heart Disease
Surgical results address only those undergoing the operative procedure, and such results thus offer a skewed and biased prognosis or outlook. Some years ago, we demonstrated that nearly 50% of infants with tricuspid atresia either died or were excluded from Fontan’s operation. Franklin and his colleagues, reviewing the combined experience of both the Great Ormond Street Hospital for Sick Children and the Brompton Hospital several years later, had virtually the same results for patients with tricuspid atresia. The results for patients with right atrial isomerism are even more disappointing. Although a Fontan operation can be carried out in some patients with right atrial isomerism with a mortality <10%, a cohort analysis showed that only 35% of all 91 patients seen at the Toronto Hospital for Sick Children with right atrial isomerism from 1970 to 1996 were alive at 5 years. Similar results have been published by Sadiq and his colleagues, reviewing the Birmingham Children’s Hospital, and from the review by Gaynor and his colleagues of the Children’s Hospital of Philadelphia.

One can use any of a number of maneuvers to enhance cohort capture or inclusion. By reviewing the fate of a large cohort, one can identify specific morphological risk factors and develop strategies to neutralize them. In this regard, the Congenital Heart Surgeons Study has provided wonderful information on outcomes in a variety of malformations, including transposition of the great arteries, hypoplastic left heart syndrome, interruption of the aortic arch, neonatal coarctation, critical pulmonary stenosis, and pulmonary atre-
sia and intact ventricular septum. The US Natural History Study of Congenital Heart Disease Nos. 1 and 2, the Baltimore-Washington Infant Study, and the New England Regional Infant Cardiac Program are but some of the important summaries of clinical outcomes addressing both specific lesions and outcomes of infants with congenital heart disease in disparate areas of the United States.\textsuperscript{155}–\textsuperscript{160}

Other strategies to reduce mortality and to enhance cohort inclusion are regionalization and the development of standards for practice.\textsuperscript{161}–\textsuperscript{164} There is increasing evidence that regionalization can reduce surgical mortality and thus enhance outcomes. Data from Jenkins and her colleagues, showing in-hospital mortality for surgical repair of congenital heart defects was inversely related to caseload and that when low-volume institutions carried out presumably low-risk operations, their mortality was still higher than in the larger-volume institutions. Similar results were published by Sollano and her colleagues, reviewing volume-outcome relationships for congenital heart surgery performed in New York State from 1990 to 1995. Stark, in his Glenn lecture of 1995, “How to Choose a Cardiac Surgeon,” came to similar conclusions. Data from his analysis demonstrated that in England and Wales, surgical mortality in infants <1 year of age in the 2 high-volume centers was 6%, whereas in the 2 low-volume institutions, surgical mortality was 19%. Regionalization based on surgical mortality and length of stay, etc., has been carried out in Sweden, reducing from 4 centers to 2 those carrying out congenital heart surgery: from Stockholm, Lund, Uppsala, and Goteborg to Goteborg and Lund. Such changes require data. Fosburg, in his Presidential address, “Fulfilling Expectations,” read at the 18th Annual Meeting of the Western Thoracic Surgical Association, stated that “you cannot manage what you cannot measure.”\textsuperscript{165} He went on to say as well, “If you are not analyzing the data your program generates, the cause of your failure will remain high.” One must also be cognizant of the human factors that contribute to surgical mortality and “near misses,” and the specialty owes a debt of gratitude to Marc De Leval, who in such a thoughtful way has documented these issues in 2 provocative articles.\textsuperscript{166,167} In this regard, we are again cautioned by Fosburg, who states, “Hospitals have been quite successful at guarding hospital-specific information regarding their quality and efficiency. ... I believe in the public release of health outcomes information. It is a powerful motivator for change.”\textsuperscript{168} Thus, disclosure of health outcomes and regionalization remain both contentious and controversial, but many of the available data are compelling. This is not to suggest, however, that some low-volume institutions cannot achieve excellent results. In regard to outcome, McCrindle, in a recent commentary, stated, “However, with increasing sophistication of surgical and medical management, mortality is becoming a less prominent issue, and the focus must shift toward morbidity, functional status, quality of life, and resource demands in both the short and long term. When mortality is equivalent with different strategies, these types of outcomes must then play into the decision-making.”\textsuperscript{168}

It is difficult to prove that setting standards for training will enhance outcomes. Standards for training in pediatric cardiology and certification was formalized by the American Board of Pediatrics and specific training guidelines in pediatric cardiology by its subboard in pediatric cardiology. Certification in this specialty began in 1960, and the minimum training required was 2 years before the examination in pediatric cardiology could be taken. The period of minimum training was extended to 3 years in 1988. The Royal College of Physicians and Surgeons of Canada has certified the specialty of pediatric cardiology for >30 years and in 1996 extended its minimum period of training from 2 to 3 years before the examination could be taken. The Section of Cardiology of the American Academy of Pediatrics has provided guidelines for centers providing diagnosis and treatment.\textsuperscript{169} These recommendations have implications for training and education as well as for the quality of care. The Section states that a center should serve an area with \(\geq 30,000\) births per year. It also makes recommendations concerning caseloads. As an absolute minimum, a center providing high-quality diagnostic, interventional, and electrophysiological procedures should perform 150 catheterizations per year, with half of these performed in neonates or infants. As an absolute minimum, they recommend that 100 pediatric cardiac surgical procedures be performed per year. 75 of these with extracorporeal circulation. What about pediatric cardiac surgery? Stark takes issue with the guidelines for certification by the American Board of Thoracic Surgery.\textsuperscript{162} This board requires that a candidate must operate on 20 patients with congenital heart disease before he or she is eligible to take the examination of the American Board of Thoracic Surgery. This is clearly inadequate, and most candidates interested in a career in congenital heart surgery will take an additional 1 to 2 years of fellowship in congenital heart surgery.

**Preventive Pediatric Cardiology**

Over the past 50 years, data have been accumulating about our ability to prevent many types of pediatric heart disease.\textsuperscript{170}–\textsuperscript{178} Diphtheric heart disease, which was common in the first half of the 20th century, is now a curiosity because of the success of immunization. Rheumatic fever and rheumatic heart disease in the United States also became much less common because of advances in public health. In the early 1960s, the congenital rubella syndrome was a significant contributor to congenital cardiac malformations in the population and is now virtually gone as a result of immunization. In midcentury, endocardial fibroelastosis was the most common reason for an infant without a structural heart malformation to be admitted to the hospital with heart failure or to die of an untreatable heart disease. The cases of endocardial fibroelastosis disappeared abruptly in the mid-1970s. Nearly 25 years later, when polymerase chain reaction technology became available, it could be demonstrated that some of these cases were due to prenatal mumps virus infection. The potential for prevention of additional heart disease in the population by public health interventions in youth remains. A number of biological precursors of atherosclerosis are incompletely explored. The potential exists that immunization against additional agents could be found to prevent some subclinical inflammatory cardiovascular disease in childhood that ultimately results in cardiomyopathy or vascular abnormality in adult life.
Genetics of Congenital Heart Disease

The field of pediatric cardiology has been influenced greatly by enhanced understanding of genetics over the past 50 years. Genes code for a number of the cardiovascular abnormalities that affect children. Descriptive knowledge of pediatric heart disease associated with syndromes has been of practical importance. Cardiovascular abnormalities are prevalent in many of the chromosomal defects. The specific knowledge of gene products and of genetic mechanisms of cardiovascular abnormalities in children has revolutionized many of our diagnostic approaches and is increasingly directly enhancing options for treatment.

Conclusions

The voices of some of the giants of our specialty are now stilled: Helen Taussig, Alfred Blalock, Benjamin Gasul, William Mustard, Ed Lambert, Maurice Lev, William Rashkind, Richard Rowe, John Keith, Robert Gross, Dan McNamara, Sir Russell Brock, Richard Bonham-Carter, C. Walton Lillehei, Dwight McGoon, and Alexander Nadas, to name but a few. Fortunately, their legacy survives through their many trainees who now strive on many fronts to advance this wonderful specialty. For those of us fortunate enough to have worked with them, we are truly privileged. They are the “genetics” of what we do!

References

IV-66 Circulation

November 14, 2000


**Key Words:** defects ■ Fontan procedure ■ pediatrics ■ prostaglandins ■ transposition of great vessels